Final report-Teratologic Evaluation of FDA 71-40 (**Dilauryl Thiodipropionic Acid**) in Rabbits
7/31/73

FOOD AND DRUG
LABORATORIES, INC.

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FINAL
July 31, 1973

Teratologic Evaluation of FDA 71-40
(Dilauryl thiodipropionic acid)
in
Rabbits

RABBITS

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FOOD AND DRUG Research LABORATORIES, INC.
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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 31, 1973

Laboratory No. 0904 w
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-40 (Dilauryl thiodipropionic acid)

Examination Requested: Teratologic evaluation of FDA 71-40 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion:

On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 1000 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 161 through 166

Material : FDA 71-40

Date: June 28, 1973

Laboratory No. : 0904 w

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose ** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
161	Sham	0.0	15	10	12	8
162	6-AN*	2.5	19	10	18	10
163	FDA 71-40	10.0	29	12	22	9
164	FDA 71-40	45.0	28	14	25	13
165	FDA 71-40	216.0	17	12	15	10
166	FDA 71-40	1000.0	24	13	20	11

* Positive Control : 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

** Administered as a corn oil solution (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 161 through 166 | Table 2 | Date: June 28, 1973

Material: FDA 71-40 | Reproduction Data (Rabbits) | Laboratory No.: 0904 w

Group:	161	162	163	164	165	166
Dose (mg/kg):	Sham	6-AN**	10.0	45.0	216.0	1000.0
Pregnancies						
Total No.	10	10	12	14	12	13
Died or Aborted (before Day 29)	2	0	3	1	2	4
To term (on Day 29)	8	10	9	13	10	11
Corpora Lutea						
Total No.	165	189	211	260	202	257
Average/dam mated	11.0	9.95	7.28	9.29	11.9	10.7
Live Litters						
Total No.*	7	9	8	8	10	10
Implant Sites						
Total No.	63	76	44	59	44	59
Average/dam*	7.88	7.60	4.89	4.54	4.40	5.36
Resorptions						
Total No.*	9	21	5	13	12	14
Dams with 1 or more sites resorbed	4	7	3	6	6	5
Dams with all sites resorbed	1	1	1	3	--	1
Per cent partial resorptions	50.0	70.0	33.3	46.2	60.0	45.5
Per cent complete resorptions	12.5	10.0	11.1	23.1	--	9.09
Live Fetuses						
Total No.	54	54	36	43	32	45
Average/dam*	6.75	5.40	4.00	3.31	3.20	4.09
Sex ratio (M/F)	0.93	0.74	0.80	0.59	0.78	1.25
Dead Fetuses						
Total No.*	--	1	3	3	--	--
Dams with 1 or more dead	--	1	1	2	--	--
Dams with all dead	--	--	--	1	--	--
Per cent partial dead	--	10.0	11.1	15.4	--	--
Per cent all dead	--	--	--	7.69	--	--
Average Fetus Weight, g	38.9	30.0	33.0	39.9	39.1	38.0

* Includes only those dams examined at term.

** Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 161 through 166 — Laboratory No. 0904 w

Material FDA 71-40 — Date June 28, 1973

Table 3

Summary of Skeletal Findings* (Rabbits)

Findings / Group No.:	161	162	163	164	165	166
Dose (mg/kg):	Sham	6-AN**	10.0	45.0	21.60	1000.0
Live Fetuses Examined (at term)	54/7	54/9	36/8	43/8	32/10	45/10
Sternebrae						
Incomplete oss.		2/2		1/1	3/2	4/2
Scrambled						
Bipartite	1/1	1/1		2/2		
Fused		4/2	2/2		1/1	4/2
Extra	3/2		1/1	1/1	1/1	1/1
Missing		1/1				
Other						
Ribs						
Incomplete oss.						
Fused/split		11/5			1/1	1/1
Wavy						
Less than 12						
More than 13						
Other						
Vertebrae						
Incomplete oss.						
Scrambled		21/5				
Fused						1/1
Extra ctrs. oss.						
Scoliosis		18/7	1/1			
Tail defects		35/8				1/1
Other						
Skull						
Incomplete closure		1/1				3/1
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.						
Missing						
Extra						
Miscellaneous						

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control :2.5 mg/kg of 6-aminonicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 161 through 166 Date June 28, 1973

Material FDA 71-40 Laboratory No. 0904 w

Table 3-a

Summary of Soft Tissue Abnormalities

(Rabbits)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
162	6-AN*	2.5	Z 4251	2	Medial rotation of hind limbs
			Z 6432	4	Anopia
				2	Anopia; medial rotation of hind limbs
			Z 6433	2	Anopia; medial rotation of hind limbs; cleft palate
			Z 6435	1	Anopia
			Z 6438	1	Medial rotation of hind limbs
			Z 6439	1	Encephalocele; anopia; medial rotation of hind limbs; umbilical hernia
				1	Medial rotation of hind limbs; umbilical hernia

* Positive Control: 2.5 mg/kg Of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 161 through 166

Species Rabbits

Date June 28, 1973

Laboratory No. 0904 w

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	12	18	29**
		mg/kg	kg				
161	Sham	0.0	2.60	2.60	2.63	2.60	2.88 (8)
162	6-AN***	2.5	2.28	2.37	2.38	2.45	2.44 (10)
163	FDA 71-40	10.0	1.76	1.82	1.80	1.83	1.92 (9)
164	FDA 71-40	45.0	2.33	2.45	2.43	2.49	2.56 (13)
165	FDA 71-40	216.0	2.12	2.16	2.17	2.17	2.34 (10)
166	FDA 71-40	1000.0	2.03	2.14	2.15	2.17	2.33 (11)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

Dosage (mg/kg)	Dose (ml/kg)	Concentration (mg/ml)
$\leq$ 250	1	$\leq$ 250
251 - 500	2	125 - 250
501 - 750	3	133 - 250
751 - 1000	4	187 - 250
1001 - 1250	5	200 - 250
1251 - 1500	6	208 - 250
1501 - 1600	6.4	235 - 250

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 161

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date June 28, 1973

Laboratory No. 0904

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 4246	NP	7	0						----	
S 4247	P	12	6	3		1	2	3	40.7	
S 4248	P	13	2	--		--	--		----	Died Day 6
S 4249	NP	0	0						----	
S 4250	P	18	7	7		4	3		44.9	
S 4251	P	5	4					4	----	
S 4252	NP	11	0						----	Died Day 19
S 4253	NP	3	0						----	
S 4254	P	9	5	--		--	--		----	Died Day 12
S 4255	NP	10	0						----	
S 6441	P	19	9	8		5	3	1	43.5	
S 6442	P	13	9	8		4	4	1	44.5	Two Neonatal Deaths
S 6443	P	10	7	7		3	4		34.0	
S 6444	P	20	12	12		6	6		31.7	
S 6445	P	15	9	9		3	6		33.1	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 162

Material 6-AN

Dose 2.5 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date June 28, 1973

Laboratory No. 0904 x

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
Z 4244	NP	0	0						----	
Z 4245	NP	2	0						----	
Z 4246	NP	11	0						----	Died Day 11
Z 4247	NP	6	0						----	
Z 4248	NP	4	0						----	
Z 4249	NP	1	0						----	
Z 4250	NP	0	0						----	
Z 4251	P	20	9	5		2	3	4	36.2	Four Neonatal Deaths
Z 4252	P	13	5	5		2	3		31.0	Two Neonatal Deaths
Z 4253	NP	0	0						----	
Z 4254	P	5	4					4	----	
Z 4255	NP	13	0						----	
Z 6432	P	11	7	6		3	3	1	31.2	Five Neonatal Deaths
Z 6433	P	14	5	2		1	1	3	23.0	Two Neonatal Deaths
Z 6434	P	28	11	6		4	2	5	25.7	Two Neonatal Deaths
Z 6435	P	21	7	3	1	1	2	3	33.0	Four Neonatal Deaths
Z 6438	P	14	11	11		4	7		28.2	Eight Neonatal Deaths
Z 6439	P	10	8	7		3	4	1	26.8	Seven Neonatal Deaths
Z 6440	P	16	9	9		3	6		35.3	Nine Neonatal Deaths

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 163

Material FDA 71-40

Dose 10.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date June 28, 1973

Laboratory No. 0904 w

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
W 4001	NP	3	0						----	
W 4002	NP	3	0						----	
W 4003	NP	2	0						----	
W 4004	P	6	2					2	----	
W 4005	P	8	4	4		2	2		31.2	
W 4006	NP	3	0						----	
W 4007	NP	2	0						----	
W 4008	NP	6	0						----	
W 4009	P	17	4	3		2	1	1	38.4	
W 4010	NP	5	0						----	Died Day 9
W 4011	NP	10	0						----	
W 4012	P	10	5	5		2	3		28.0	
W 4013	NP	7	0						----	
W 4014	P	13	5	--		--	--		----	Sacrificed Day 12
W 4015	NP	7	0						----	
W 4061	NP	9	0						----	Died Day 28
W 4062	P	13	5	3		--	--	2	----	Died Day 16
W 4063	NP	2	0						----	
W 4064	P	14	5	5		2	3		32.6	
W 4065	NP	5	0						----	Died Day 23
W 4066	P	6	4	2		1	1	2	44.3	
W 4067	P	16	5	5		2	3		34.7	
W 4068	NP	3	0						----	
W 4069	NP	0	0						----	
W 4070	NP	2	0						----	
W 4088	NP	2	0						----	Died Day 27
W 4089	P	6	3	--		--	--	3	----	Died Day 18
W 4090	P	10	5	5		2	3		35.3	
W 4091	P	21	10	7	3	3	4		20.0	Six Neonatal Deaths

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 164

Material FDA 71-40

Dose 45.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date

Laboratory No. 0904 w

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
W 4016	NP	2	0						----	
W 4017	NP	7	0						----	Died Day 19
W 4018	NP	5	0						----	
W 4019	NP	0	0						----	
W 4020	NP	2	0						----	
W 4021	NP	5	0						----	
W 4022	P	26	7						----	Died Day 25
W 4023	NP	12	0						----	
W 4024	P	8	3	2		0	2	1	43.8	
W 4025	P	20	4	4		3	1		46.1	
W 4026	NP	4	0						----	
W 4027	NP	5	0						----	Died Day 6
W 4028	P	20	10	9		4	5	1	36.1	
W 4029	P	25	4	4		1	3		42.1	
W 4030	NP	0	0						----	
W 4071	NP	4	0						----	
W 4072	NP	0	0						----	
W 4073	P	8	2					2	----	
W 4074	NP	7	0						----	
W 4075	P	22	8	8		2	6		32.1	One Neonatal Death
W 4076	P	4	2					2	----	
W 4077	P	15	5		1			4	----	
W 4078	P	10	3	3		1	2		45.9	
W 4094	P	8	2		2				----	
W 4095	NP	6	0						----	
W 4096	P	8	3					3	----	
W 4097	P	14	7	7		3	4		33.5	
W 4098	P	13	6	6		2	4		39.4	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 165

Material FDA 71-40

Dose 216.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date

Laboratory No. 0904 w

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
W 4031	NP	10	0						----	
W 4032	NP	5	0						----	
W 4033	P	--	7	3		1	2	4	33.2	
W 4034	P	10	3	2		1	1	1	43.9	
W 4035	P	8	7	5		3	2	2	37.7	
W 4036	P	13	3	3		2	1		34.4	
W 4037	P	6	3	1		0	1	2	45.4	
W 4038	NP	9	0						----	
W 4039	NP	6	0						----	
W 4040	P	20	3	3		1	2		38.0	
W 4041	P	16	3	3		0	3		41.8	
W 4042	P	27	4	3		2	1	1	39.8	
W 4043	P	13	5						----	Died Day 28
W 4044	NP	2	0						----	
W 4045	P	20	8	8		3	5		29.3	
W 4079	P	17	3					3	----	Aborted Day 27
W 4080	P	20	3	1		1	0	2	47.5	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 166

Material FDA 71-40

Dose 1000.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date

Laboratory No. 0904 w

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
W 4046	NP	6	0						----	
W 4047	P	15	6	6		4	2		33.0	
W 4048	NP	0	0						----	
W 4049	NP	3	0						----	
W 4050	P	17	8	6		2	4	2	23.4	Five Neonatal Deaths
W 4051	NP	15	0						----	Died Day 25
W 4052	P	17	4						----	Died Day 17
W 4053	P	25	3	3		2	1		42.0	
W 4054	NP	0	0						----	
W 4055	P	23	7	4		1	3	3	35.2	
W 4056	P	9	2	2		2	0		46.3	
W 4057	NP	17	0						----	
W 4058	NP	5	0						----	
W 4059	NP	3	0						----	
W 4060	NP	7	0						----	
W 4081	P	12	1	1		--	--		----	Aborted Day 20
W 4082	NP	9	0						----	
W 4083	P	5	5					5	----	
W 4084	P	14	4	4		3	1		43.6	
W 4085	P	12	5	2		0	2	3	52.7	
W 4086	P	13	6	6		4	2		23.7	
W 4087	P	16	6	5		3	2	1	36.0	One Neonatal Death
W 4092	NP	0	0						----	Died Day 11
W 4093	P	14	7	7		4	3		43.7	

* P = Pregnant; NP = Not Pregnant